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Modeling of the Toxicity of Chemicals to Hydra attenuata: A DFT Study

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ABSTRACT

The main aim of study was to assess the comparative use of molecular and quantum chemical descriptors in developing efficient QSARs for predicating the toxicity of chemicals towards *Hydra attenuata*. The comparison of the QSARs [$pIGC_{50}$ = -22.185 E_{LUMO} + 0.020 α +1.128 , R^2_{adj} = 0.932, RSS = 6.997, F = 398.611], [$pIGC_{50}$ = 1.032 ω + 0.022 α – 1.019, R^2_{adj} = 0.9284, RSS =0.7.3719, F= 376.9091], [$pIGC_{50}$= -38.098E_{LUMO} + 3.375, R^2_{adj} = 0.8895, RSS = 11.3781, F = 234.3418] and [$pIGC_{50}$= 0.019 ω – 0.093, R^2_{adj} = 0.8711, RSS = 12.998, F = 200.675] reveals that E_{LUMO} is slightly a better descriptor for parameterization of electrophilicity of the test molecules, partially responsible for their toxic action. The overall results indicate that E_{LUMO} and polarizability are the better descriptors of the electrophilic reactivity and lipophilicity, respectively, for mapping toxicity of chemicals towards *Hydra attenuata.*

Keywords: Quantitative-structure-activity relationship, Density Functional theory, electrophilicity, hydrophobicity, *Hydra Attenuata*

INTRODUCTION

QSARs developed by using molecular and quantum chemical descriptors are powerful tools for exotoxicological studies in predicating the toxicological effects of chemicals. The main objective of QSAR studies in toxicology is to develop mathematical models for prediction of adverse effects of chemicals on living organism. Toxicity caused by a chemical compound is a function of its structural features. Therefore, any minor variation in its structural feature can make large change in its toxicity character. Suitable QSAR models can be employed to relate the biological activity of series of chemicals to their physiochemical and structural parameters. The information obtained from QSAR studies, can provide a deeper knowledge for molecular design, medicinal chemistry and mechanism of biological activity [1-5]. A large number of QSAR for modeling toxicity of organic chemical compounds have been reported in the literature [6-17]. The quality of QSAR models mainly depends on the proper selection of descriptors of biological activity, the type of statistical procedure employed and finally on the nature and mode of biological activity under investigation. The basic assumption for QSAR models is that the magnitude of a biological activity of a molecule is related to some empirical property or theoretical parameter describing the chemical structure of the molecule under investigation [18]. Therefore, in order to expect an accurate prediction of the biological activity of a set of bioactive molecules using QSAR models, the proper choice of the descriptor or a set of descriptors in developing the QSAR equations is of paramount importance. The descriptors chosen may include physical properties of molecules, physico-chemical parameters associated with various functional groups, electronic parameters calculated by quantum chemical methods or topological indices defined on chemical graphs of molecules using mathematical techniques [19-37].

Hydra attenuata is a metazoan, commonly found in slow-moving waters and belongs to freshwater Cnidarian family [38]. Since all the cells of hydra are in contact with its immediate aqueous environment, it is very sensitive and susceptible to minute amounts of environmental toxicants present in its surrounding medium[39]. This feature has enabled hydra to be a useful environmental toxicological model for the study of the effects of environmental toxicity. In addition to its remarkable sensitivity towards the surrounding medium, its reproducibility by means of asexual reproduction yielding clones of individual organisms, is another important advantage [40,41]. The important toxicity markers include the change in the external morphology, anatomy, physiology or total population in the hydra bioassays. Many studies have exploited the use of the hydra bioassay to determine the toxicity of various compounds including chlorinated phenols [42], heavy metals [38], and estrogenic compounds[43]. The objective of this work was to quantify the toxicity (in terms of 50% population growth inhibition (pIGC50)) of a series of chemicals by using various combinations of descriptors parameterizing major molecular properties responsible for their toxic effects. In view of this, we have developed QSAR models for 30 compounds using DFT level of theory.

Density functional theory (DFT) was founded within the two basic theorems provided by Hohenberg and Khon in the 1960's [44,45]. The performance of the DFT method in the description of structural, energetic, and magnetic molecular properties is well established [46-47]. DFT methods are, in general, capable of generating a variety of isolated molecular physico-chemical and quantum mechanical descriptors, such as highest occupied molecular orbital (HOMO)energies, lowest unoccupied molecular orbital (LUMO) energies, global hardness (?), softness (**S**), electronegativity (w) , chemical potential (**μ**), electrophilicity index (w) electrofugality (**DE_e**), nucleofugality (**DE_e**), total energy(au) (**E**), molecular weight (**M**), single point energy (**SPE**) and polarizability (a) quite accurately[19,48]. Recent studies have shown that the quantum chemical descriptors based on the DFT method are better than those based on the semi-emperical method in establishing optimal QSAR model equations [49-57].

MATERIAL AND METHOD

The experimental toxicity data such as negative logarithm of 50% population growth inhibition ($pIGC_{50}$) for molecules were obtained from the literature [58-61] and is reported in Table 1. The toxicity data ($pIGC_{50}$ values) of the test molecules were converted into mol/l for modeling purpose. For all molecules studied here, the quantum chemical computations were performed using Gaussian-03 quantum chemistry package [62]. The initial geometries were optimized by the DFT method, employing Becke's three-parameter hybrid functional (B3LYP) and 6-311G (d, p) basis set [53,63]. Moreover, the fre-

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quency calculations were performed to confirm that the optimized geometries are at an energy minimum. An in-house statistical package was used for regression analysis to develop the model QSAR equations. Model adequacy was quantified with the r^2 value (squared coefficient of determination) adjusted for degrees of freedom. The number of observations (n), residual sum of squares (RSS) and Fisher statistic (F) are also reported.

Theoretical Background

Parr and co-workers [64] have defined electrophilicity index (?) as a measure of the decrease in energy due to the maximal transfer of electrons from donor to an acceptor molecule, and is given as;

$$W = \frac{\mu^2}{2\eta}$$

where μ and η are chemical potential and hardness respectively . Chemical potential [63],hardness [64,65] and softness [66] can be expressed in terms of ionization energy (I) and electron affinity (A) as ;

$$\mu = \left(\frac{\partial E}{\partial N}\right)_{v(r)} \approx -\frac{I+A}{2}, \quad \eta = \frac{1}{2}\left(\frac{\partial \mu}{\partial N}\right)_{v(r)} \approx \frac{I-A}{2} \quad \text{and} \quad S = \frac{1}{2\eta} = \left(\frac{1}{2}\left(\frac{\partial \mu}{\partial N}\right)_{v(r)}\right)^{-1}$$

In terms of the Koopmans' approximation [67], the ionization energy (I) and electron affinity (A) can be written as the eigen value of the HOMO and LUMO with change of sign; [68]

$$I \approx -E_{HOMO} \qquad A \approx -E_{LUMO} \qquad (3)$$

Polarizability is the measure of the change in a molecule's electron distribution in response to an applied electric field, which can also be induced by electric interactions with solvents or ionic reagents [69-71]. It represents a second order variable in energy;

$$\alpha_{a,b} = -(\partial^2 E / \partial F_a \, \partial F_b); \quad a, b = x, y, z$$

and is calculated as fallows

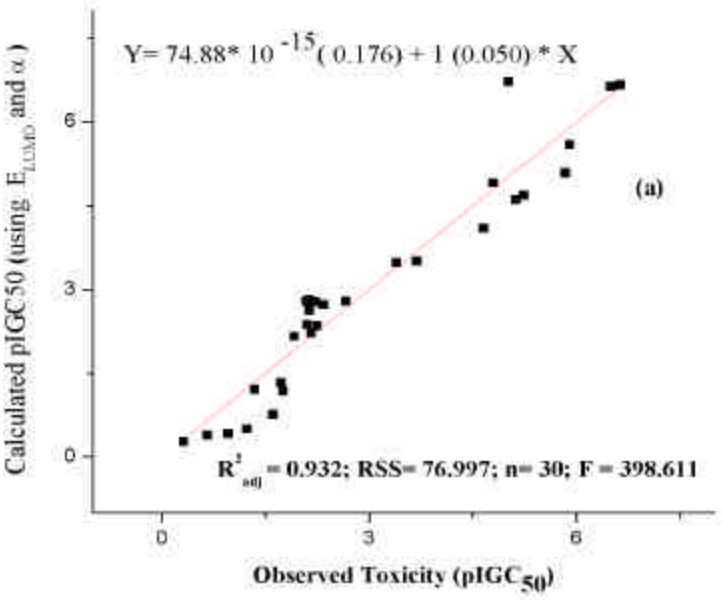
$$\langle a \rangle = 1/3 \, (a_{xx} + a_{yy} + a_{zz}) \qquad (4)$$

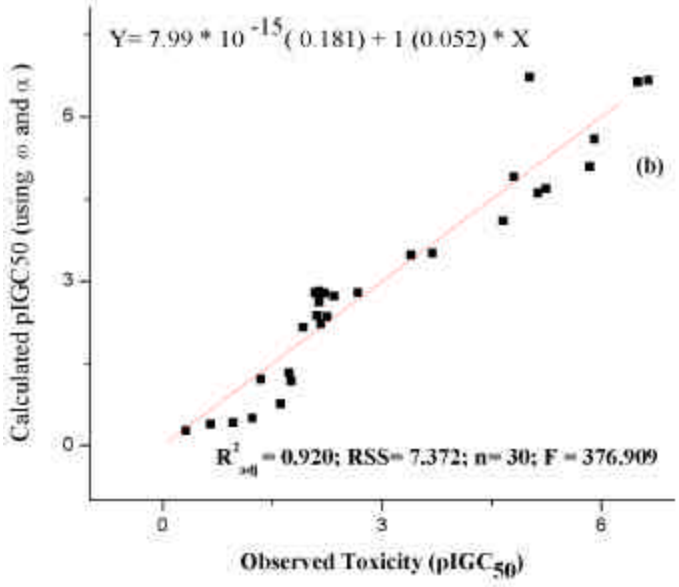
RESULT AND DISCUSSION

The quantum chemical descriptors like LUMO energy, HOMO energy, ionization energy, electron affinity, chemical potential, hardness, softness, polarizability, electrophilicity, single point energies, total energies etc., calculated from optimized geometries using equations 1-4, and other structural descriptors, such as molecular weight, of a series of organic molecules are given in Table 1 and Table 2. The main objective of this work was to develop efficient QSAR models, which are predictive of the toxicity of various organic compounds towards *Hydra attenuata*, by using a combination of molecular and quantum chemical descriptor calculated at B3LYP/6311-G (d, p) level of theory. The general regression equations of the models constructed for the whole set of compounds are given in Table 3. From our preliminary calculations, it becomes clear that among the set of calculated descriptors, only the E_{LUMO}, ω and α contribute significantly to the toxicity behavior of the test compounds as is evident from the R^2_{adj} values (see Table 3). In order to analyze the cumulative effect of the descriptors in enhancing the efficiency of the model equations, a two and three parameter regression analysis was performed of the test compounds for estimating their toxicity. In two parameter regression equations, a combination of parameters such as (E_{LUMO}, α), (E_{LUMO}, W) show better results as compared to the combination of (ω, α), and (ω, W), suggesting that E_{LUMO} is marginally a better descriptor than ω for parameterization of electrophilic reactivity. The representative plots are presented in Figures 1 and Figure 2, and the corresponding calculated toxicity values ($PIGC_{50}$) given in Table 4. The plots of observed toxicity values ($PIGC_{50}$) versus the predicted ones, calculated on the basis of multiple parameter regression equations using the combination of three parameter E_{LUMO}, ω and α, show slightly better results as compared to a combination of E_{LUMO}, ω and W, as is evident from R^2_{adj} values [R^2_{adj} = 0.963; R^2_{adj} = 0.942, respectively] (Figures 3).The corresponding observed and calculated toxicity values ($PIGC_{50}$), are presented in Table 4. These results indicate that in case of three parameter regression models, using polarizability (α) in combination with other quantum chemical descriptors gives superior results as compared to using W for modeling hydrophobicity.

CONCLUSION

Quantitative relationships between molecular and quantum chemical descriptors and the toxicity of chemical compounds towards *Hydra attenuata* was investigated by using DFT-B3LYP/6-311G (d, p) level of theory. Our main conclusion is that good QSAR model equations for predication of toxicity of





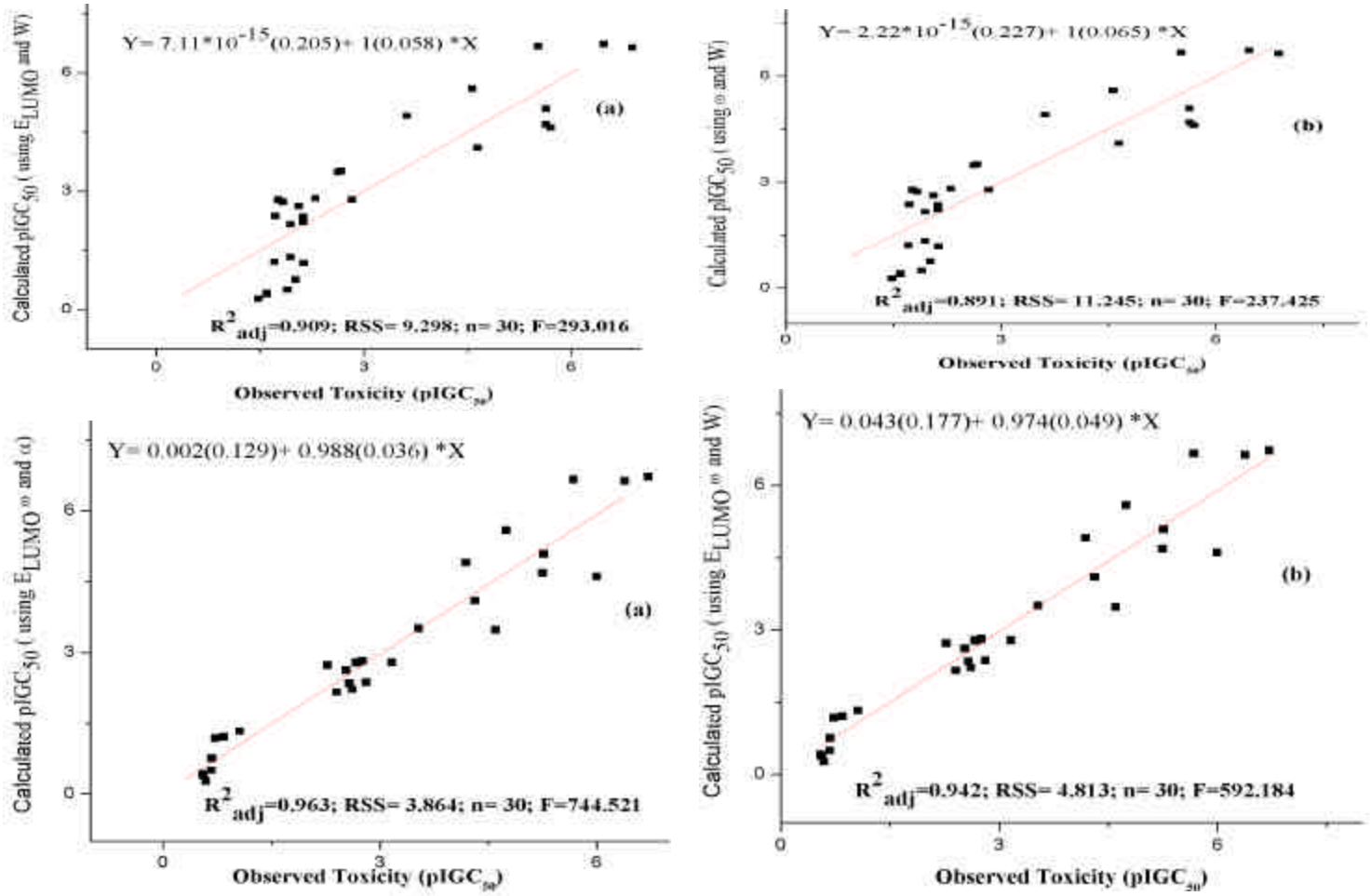


Fig 1: Observed and calculated $pIGC_{50}$ values (a) using E_{LUMO} and a descriptors and (b) using w and a descriptor in two parameter regression model for complete set of molecules

Table 1: Calculated single point energies, total energies, molecular weight, polarizability of Compounds

Comp. No.	Compound name	$pIGC_{50}$*	SPE (Kcal/mol)	E (au)	a (au)	Mol. Weight
1	Ethylene glycol	0.27	53.19	-230.16	30.22	62.04
2	Propylene glycol	0.39	71.03	-269.46	40.48	76.05
3	Hexylene glycol	1.33	123.97	-387.32	72.84	118.10
4	Ethylene glycol monomethyl ether	0.42	71.05	-269.44	50.62	76.05
5	Ethylene glycol monomethyl ether acetate	2.22	112.97	-461.35	85.31	132.12
6	Ethylene glycol monoethyl ether	1.21	88.96	-308.73	62.27	90.07
7	Ethylene glycol monoethyl ether acetate	2.35	112.97	-461.35	88.00	132.08
8	Ethylene glycol monobutyl ether	2.16	124.83	-387.30	79.17	118.10
9	Ethylene glycol monophenyl ether	2.62	142.72	-426.59	85.31	132.12
10	Ethylene glycol diacetate	2.82	101.07	-535.42	82.25	146.06
11	Diethylene glycol	0.5	91.83	-383.93	56.29	106.06
12	Diethylene glycol monomethyl ether	0.76	109.62	-423.21	67.86	120.08
13	Diethylene glycol monoethyl ether	1.18	127.51	-462.50	71.62	134.09
14	Diethylene glycol dibutyl ether	2.79	234.88	-698.22	95.31	218.19
15	o-Xylene	2.78	97.94	-310.74	91.29	106.08
16	m-Xylene	2.79	97.52	-310.74	87.08	106.08
17	p-Xylene	2.79	97.48	-310.74	87.48	106.08
18	Ethylene glycol tetra-acetic acid	4.1	256.60	-1409.29	141.40	380.14
19	Ethylene glycol monosalicylate	3.48	113.55	-649.69	121.03	182.06
20	Phenol	2.37	65.76	-307.37	87.77	94.04
21	4-Chlorophenol	3.51	59.75	-766.97	127.41	128.00
22	3,5-Dichlorophenol	4.91	53.69	-1226.57	151.37	161.96
23	2,3,5-Trichlorophenol	5.6	47.78	-1686.17	174.99	195.92
24	2,3,4,5-Tetrachlorophenol	6.67	41.72	-2145.76	186.51	229.89
25	2,3,4,5-Tetrachloroanisole	5.09	59.09	-2185.03	158.65	243.90
26	2,3,5,6-Tetrachloroanisole	4.69	59.14	-2185.03	138.76	243.90
27	Tetrachloro-1,2-benzoquinone	4.61	29.33	-2219.74	133.89	243.87
28	Pentachlorophenol	6.73	35.69	-2605.35	119.24	263.85
29	Pentachlorophenyl acetate	6.64	58.55	-2757.96	164.27	305.86
30	p-Phenylenediamine	2.73	83.93	-342.83	94.55	108.07

Table 2: Calculated HOMO energies, LUMO energies, ionization energies, electron affinity, electronegativities, hardness, softness, chemical potential, and electrophilicity index of compounds

Comp. No.	pIGC50*	HOMO (au)	E_{LUMO}(au)	I(eV)	A(eV)	c (eV)	h (eV)	S(eV)	w (eV)
1	0.27	-0.259	0.075	0.259	-0.075	2.506	4.554	0.110	0.690
2	0.39	-0.264	0.079	0.264	-0.079	2.516	4.671	0.107	0.678
3	1.33	-0.249	0.065	0.249	-0.065	2.495	4.272	0.117	0.729
4	0.42	-0.248	0.078	0.248	-0.078	2.320	4.431	0.113	0.607
5	2.22	-0.261	0.017	0.261	-0.017	3.320	3.769	0.133	1.462
6	1.21	-0.245	0.069	0.245	-0.069	2.407	4.273	0.117	0.678
7	2.35	-0.257	0.017	0.257	-0.017	3.267	3.738	0.134	1.428
8	2.16	-0.243	0.019	0.243	-0.019	3.050	3.568	0.140	1.304
9	2.62	-0.243	0.017	0.243	-0.017	3.076	3.536	0.141	1.338
10	2.82	-0.275	0.016	0.275	-0.016	3.522	3.948	0.127	1.571
11	0.5	-0.245	0.077	0.245	-0.077	2.284	4.384	0.114	0.595
12	0.76	-0.243	0.079	0.243	-0.079	2.234	4.380	0.114	0.570
13	1.18	-0.241	0.079	0.241	-0.079	2.206	4.357	0.115	0.558
14	2.79	-0.238	0.008	0.238	-0.008	3.139	3.349	0.149	1.471
15	2.78	-0.230	0.007	0.230	-0.007	3.028	3.219	0.155	1.424
16	2.79	-0.229	0.007	0.229	-0.007	3.026	3.217	0.155	1.423
17	2.79	-0.226	0.007	0.226	-0.007	2.975	3.166	0.158	1.397
18	4.1	-0.207	-0.010	0.207	0.010	2.956	2.676	0.187	1.633
19	3.48	-0.229	-0.037	0.229	0.037	3.609	2.613	0.191	2.493
20	2.37	-0.219	0.001	0.219	-0.001	2.976	2.991	0.167	1.481
21	3.51	-0.224	-0.015	0.224	0.015	3.257	2.837	0.176	1.870
22	4.91	-0.244	-0.027	0.244	0.027	3.683	2.949	0.170	2.300
23	5.6	-0.248	-0.037	0.248	0.037	3.882	2.876	0.174	2.620
24	6.67	-0.246	-0.056	0.246	0.056	4.110	2.597	0.193	3.253
25	5.09	-0.255	-0.044	0.255	0.044	4.065	2.861	0.175	2.888
26	4.69	-0.256	-0.044	0.256	0.044	4.075	2.884	0.173	2.878
27	4.61	-0.270	-0.060	0.270	0.060	4.490	2.859	0.175	3.525
28	6.73	-0.250	-0.053	0.250	0.053	4.130	2.686	0.186	3.174
29	6.64	-0.269	-0.063	0.269	0.063	4.510	2.798	0.179	3.635
30	2.73	-0.170	0.012	0.170	-0.012	2.151	2.485	0.201	0.931

Table 3: One and two parameter regression equations obtained by total regression of whole set of Compounds:

Equations	R^2	RSS	F
-5.537 HOMO + 1.675	0.0320	86.2252	0.1003
-38.098E_{LUMO} + 3.375	0.8895	11.3781	234.3418
-2.405χ– 4.621	0.7810	22.5384	104.4386
-2.299 η – 10.909	0.7034	30.5829	69.7622
53.954 S – 5.158	0.6859	30.3269	64.3366
0.019 ω – 0.093	0.8711	12.7743	205.6752
-0.011W + 3.981	0.5920	41.9913	43.0859
-0.010 SPE+ 3.995	0.0436	78.4387	2.3231
-0.002 E + 1.137	0.7746	23.1980	100.6732
0.044 α - 1.437	0.8689	13.4986	193.1304
-7.021 HOMO + 0.044 α – 3.148	0.8733	13.0355	200.9841
-22.185 E_{LUMO} + 0.020 a +1.128	0.9320	6.7998	398.6109
-1.027 χ + 0.029 α -3.227	0.9177	8.4718	324.3394
-0.601 η+ 0.035 α +1.499	0.8829	12.0524	219.6654
13.033 S + 0.036 α -2.618	0.8808	12.2651	215.3707
1.032 ω + 0.022 α – 1.019	0.9201	7.3719	376.9091
0.0004W + 0.038 α – 1.485	0.8766	12.6992	207.0508
-0.004 SPE + 0.043 α – 1.005	0.8766	12.6931	207.1509
-0.008 E + 0.029 α – 0.788	0.9129	10.9610	305.1016
-4.911 HOMO -38.077 E_{LUMO} + 2.18	0.8924	11.0775	241.4615
-2.294 S – 39.367 E_{LUMO} + 3.735	0.8897	11.3504	234.9822
0.825 ω – 22.275 E_{LUMO} + 1.835	0.9066	9.6129	282.5145
0.005 W- 32.228 E_{LUMO} + 2.514	0.9097	9.2984	293.0166
-0.001 SPE -37.692 E_{LUMO} + 3.509	0.8909	11.2256	237.9059
-0.0008E- 26.524 E_{LUMO} + 2.501	0.9386	6.3169	444.5382
-0.141 HOMO + 0.019 W - 0.126	0.5921	41.9907	43.0863
-32.228 E_{LUMO} + 0.005 W + 2.514	0.9097	9.2985	293.0165
-1.813 χ + 0.007 W – 0.4008	0.8356	16.9196	148.4205
-1.598 η +0. 010W + 6.878	0.8060	19.9626	121.5258
36.839 S +0.010W – 4.219	0.7908	21.5244	110.6783
1.606 ω +0. 004W – 0.4093	0.8907	11.2460	237.4247
-0.016SPE + 0022W + 1.127	0.7842	22.2152	106.3658
-0.002 E + 0.003W + 0.858	0.7795	22.6926	103.3658

Table 4 Observed and calculated Values of $pIGC_{50}$ for the complete set of molecules using one, two parameter and three parameter regression equations.

Comp. No.	Observed	Calculated			$pIGC_{50}$		
	pIGC50*	E_{LUMO} a	E_{LUMO} W	w α	w W	E_{LUMO} w α	E_{LUMO} wW
1	0.27	0.085	0.404	0.378	0.979	0.291	0.591
2	0.39	0.211	0.348	0.598	1.022	0.434	0.556
3	1.33	1.191	1.009	1.386	1.294	1.238	1.058
4	0.42	0.457	0.400	0.756	0.910	0.600	0.547
5	2.22	2.531	2.653	2.426	2.536	2.493	2.615
6	1.21	0.898	0.761	1.094	1.086	0.968	0.841
7	2.35	2.570	2.627	2.452	2.481	2.513	2.577
8	2.16	2.348	2.500	2.123	2.218	2.247	2.405
9	2.62	2.523	2.640	2.298	2.336	2.409	2.529
10	2.82	2.488	2.752	2.470	2.775	2.515	2.760
11	0.5	0.584	0.566	0.873	1.026	0.704	0.671
12	0.76	0.786	0.582	1.109	1.048	0.889	0.677
13	1.18	0.860	0.648	1.183	1.093	0.951	0.723
14	2.79	2.934	3.374	2.663	2.940	2.788	3.162
15	2.78	2.867	2.827	2.523	2.358	2.690	2.688
16	2.79	2.779	2.827	2.426	2.356	2.609	2.687
17	2.79	2.787	2.826	2.409	2.314	2.600	2.670
18	4.1	4.291	4.777	3.877	3.931	3.971	4.313
19	3.48	4.452	4.619	4.301	4.418	4.429	4.600
20	2.37	2.937	2.974	2.502	2.394	2.732	2.812
21	3.51	4.114	3.662	3.803	3.172	3.914	3.536
22	4.91	4.867	4.207	4.792	4.017	4.774	4.191
23	5.6	5.579	4.701	5.658	4.684	5.540	4.744
24	6.67	6.231	5.474	6.572	5.854	6.373	5.677
25	5.09	5.401	5.179	5.563	5.331	5.482	5.264
26	4.69	4.977	5.162	5.101	5.315	5.092	5.247
27	4.61	5.235	5.684	5.658	6.354	5.595	5.997
28	6.73	4.778	5.563	4.963	5.881	6.015	6.713
29	6.64	5.932	6.095	6.462	6.812	6.277	6.385
30	2.73	2.817	2.668	2.088	1.574	2.378	2.275

***** *taken from ref [58-61]*

organic compounds considered in this study can be developed by considering the hydrophobicity and electrophilicity properties, quantified by polarizability and E_{LUMO}, respectively. Among many of the physiochemical and electronic descriptors used in this study, the more important ones, polarizability (a) and energy of lowest unoccupied molecular orbital (E_{LUMO}), determine the penetrating power of chemical species through the cell membrane and their electronic interactions with the active site of action through different modes of chemical reactivity. From our results we concluded that that E_{LUMO} and a are slightly a better descriptors than ? and W for parameterization of electrophilic reactivity and hydrophobicity of the chosen data set, respectively, for the purpose of develop model equation for toxicity predication towards *Hydra attenuata*.

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